UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/941,042	08/28/2001	Mark A. Conkling	5051.471	4291

20792 7590 04/13/2004

MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 04/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/941,042	CONKLING ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-73* is/are pending in the application.

4a) Of the above claim(s) *33-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/17/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1 and 4-73 are pending.

2. It is noted that the marked-up copy of claim 8 does not correspond to the previously filed version of claim 8, as the second period in the claim is not indicated as being deleted.

3. This application contains claims 33-73 drawn to an invention nonelected with traverse in Paper No. 19. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

4. The title of the invention is still not descriptive of the instant invention, which is drawn to a nucleic acid comprising a Nic gene product responsive element, plants transformed with it and a method of reducing the level of nicotine in a tobacco plant. A new title is required that is clearly indicative of the invention to which the claims are directed. Note that titles can be up to 500 characters long.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

6. Claims 8 and 13 are objected to because of informalities. The objection is modified from the objection set forth in the Office action mailed 29 July 2004, as applied to claims 4, 8, 11-13, 18 and 22-32. Applicant's arguments filed 30 January 2004 have been fully considered but they are not persuasive.

Applicant urges that the informalities have been corrected as suggested (response pg 15).

This is not found persuasive because the following remains or is new:

In claim 8, the second recitation of "microparticle" in line 2 is misspelled.

In claim 13, either "comprises" in line 4 should be replaced with --comprise-- or an article should be inserted before the first "tobacco" in line 3.

Claim Rejections - 35 USC § 112

7. Claims 1 and 4-32 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid of SEQ ID NO:1, does not reasonably provide enablement for 200 nucleotide fragments of SEQ ID NO:1, an "active fragment of SEQ ID NO:1, nucleic acids that hybridize to SEQ ID NO:1 and are responsive to a Nic gene product, or nucleic acids of any function that have 95% identity to SEQ ID NO:1, or 20-455 nucleotide long fragments of SEQ ID NO:1, or an "active fragment of SEQ ID NO:1, methods of using the nucleic acids to reduce the levels of nicotine in a tobacco plant, and plants thereby produced. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the Office action mailed 29 July 2004, as applied to claims 1-32. Applicant's arguments filed 30 January 2004 have been fully considered but they are not persuasive.

Applicant urges that they provide fragments of 20-455 nucleic acids throughout the specification (response pg 16).

This is not found persuasive because the specification does not teach any 20 or 200 nucleotide long fragments of SEQ ID NO:1 that are "responsive to a Nic gene product" or that act as transcription factor decoys.

Applicant urges that the phrase "responsive to a Nic gene product" is defined to mean, for example, "increase or decrease transcription of an operatively associated gene and hence increase or decrease the level of the encoded protein of interest in the host cells" (response pg 17).

This is not found persuasive because, as stated in the 35 USC 112, 2nd paragraph rejection below, it is unclear what is means for a nucleic acid to be responsive to a *Nic* gene product. If the *Nic* gene product binds to the nucleic acid, it is the *Nic* gene product that responds to the nucleic acid - the nucleic acid itself does not do anything to "respond" to the gene product. The nucleic acid is SEQ ID NO:1 is a promoter that is bound by a *Nic* gene product, which then interacts with the transcription machinery to increase or decrease transcription of the operatively associated gene; SEQ ID NO:1 itself does not do anything.

Applicant urges that one approach for reducing the level of a biological product, such as nicotine, is to reduce the amount of a required enzyme in the biosynthetic pathway leading to that product; the examples assessed GUS activity and the claims have been amended to recite an active fragment (response pg 17).

This is not found persuasive. In none of the examples was the molecular decoy approach used. Example 1 characterized the minimal sequence for the NtQPT1 promoter by deletion analysis to show that the -586 to -2000 region produced the highest expression levels of GUS and in example 2 deletion constructs were transformed into tobacco plants a to show that *Nic* gene products bound between -1000 and -600 or -700 bp of the NtQPT1 promoter. In none of these examples was the level of nicotine reduced.

Applicant urges that the specification provide guidance for hybridization and amplification conditions on pg 17-18 and that one of skill in the art could readily follow these procedures; the claims have been amended to recite that the conditions are stringent (response pg 18).

This is not found persuasive because the claims do not recite the hybridization and wash conditions and the specification does not teach where to find nucleic acids that hybridize to SEQ ID NO:1 under those conditions and that are "responsive to a Nic gene product". Furthermore, the specification odes not teach any nucleic acid with 95% identity to SEQ ID NO:1.

Applicant urges that application of the current technology requires routine, not undue, experimentation, and that suppression has been used as a tool to identify gene function, citing Sharma et al and Mann et al, and that in plants DsRNA is more efficient than post-transcription suppression and that a high percentage of transgenic lines show a significant reduction in target gene product, citing Waterhouse et al (response pg 18).

This is not found persuasive. The experiments of Sharma et al were done in extracts of animal cells not in whole plants. The decoy method and sense or antisense gene suppression are different methods; in the former an overabundance of a portion of the promoter results in the inability of a transcription factor to activate the transcription machinery, while in the latter an overabundance of the RNA encoding the gene product results in an inability of the product to be made. Mann et al and Waterhouse et al could not considered because they were not sent.

Use of molecular decoys has only been done using short dsDNAs transiently transfected into cells (see, e.g., Morishita et al, 1998, Circulation Res. 82:1023-1028, paragraph spanning pg 1023-1024 and paragraph spanning the columns on pg 1026). Transformation of a plant with a

molecular decoy, wherein the decoy is present is integrated in multiple copies in the plant genome, has not been done. The instant specification fails to provide guidance for how many copies of the *Nic* gene product responsive element are required to reduce the levels of nicotine in tobacco.

The specification fails to teach transformation of a tobacco plant with a linear construct or the integration into the plant genome of a short dsDNA transfected into a plant. Note that integration of such construct is necessary for regeneration of a transformed cell into a whole plant that has reduced levels of nicotine and for production of seed that can produce such a plant. Claim 28 claims a tobacco plant comprising a circular construct. The specification fails to teach autonomously replicating circular recombinant constructs for plant transformation.

Applicant urges that the molecular decoy approach has advantages over suppression including that it is easier to reproduce, and the approach claimed in claims 11 and 24 requires only that a binding site be identified in the regulatory region of one regulated gene; US patents 6,060,310 and 6,262,033 illustrate this approach (response pg 18-19).

This is not found persuasive. Neither 6,060,310 nor 6,262,033 are drawn to plants nor stable transformation with a construct that acts as a molecular decoy. Both 6,060,310 and 6,262,033 are drawn to administration of oligonucleotides to animal cells. Thus, neither 6,060,310 nor 6,262,033 can be relied upon for enablement of the instant application. The instant specification fails to make up for the deficiencies in the teachings of these patents or any of the prior art.

Applicant urges that a reduction to practice is not necessary and the examples teach assessment of GUS activity in plant parts transformed with different NtQPT1 truncation constructs, thus showing the application is enabled (response pg 19).

This is not found persuasive because assessment of GUS activity as taught in the specification is not reduction of nicotine levels by transformation with molecular decoys. The examples teach that SEQ ID NO:1 and certain fragments of it act as a promoter and that transcription from certain large regions of the promoter requires the *Nic*$^+$ gene product. A molecular decoy approach, as instantly claimed, would require transformation of tobacco plants with a construct comprises an unknown number of copies of a portion of unknown size of SEQ ID NO:1 into plants so that the presence of the construct in the nucleus would result in the *Nic*$^+$ gene products binding to that construct instead of the "real" QPT1 promoter, such that transcription of QPT1 gene does not occur. Applicant has not taught what fragment(s) the method would require, much less 20 nucleotide long ones, nor how many copies would be required to reduce QPTase levels.

Applicant urges that the NtQPT1 cis-acting element is located between -586 and -2000 5' of the transition start site and the Nic gene products bind between -1000 and -600 and -700; thus the application provides enablement for a method of making a transgenic tobacco plant with a reduced amount of nicotine. Applicant urges that one of skill in the art would be able to ascertain which pieces of the given sequence have competitive inhibition so as not to inactivate QPTase [sic] (response pg 19-20).

This is not found persuasive. The molecular decoy approach, as taught in the prior art, involves transient transfection of oligonucleotides into cells or exposure of cell extracts to the

oligonucleotides. None of the prior art (nor the art since) teaches transformation of plants with a construct comprising copies of a portion of a promoter such that the presence of the construct results in a lack of transcription of a target gene. There are any, many more steps between applicant's teachings and stable reduction of nicotine levels in a tobacco plant, including determination of 20 nucleotide long fragments that reduce the level of nicotine in a plant and do so without negatively affecting other functions in the plant, how many copies of that fragment would be required to reduce QPTase levels, and if it is even possible to do what Applicant claims. Applicant has also not taught autonomously replicating circular recombinant constructs for plant transformation, as requires by claim 28.

8. Claims 1 and 4-32 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action mailed 29 July 2004, as applied to claims 1-32, due to Applicant's amendment of the claims. Applicant's arguments filed 30 January 2004 have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of DNA molecules that comprise 20-455 nucleotide fragments of SEQ ID NO:1, that hybridize to SEQ ID NO:1 and are responsive to a *Nic* gene product, or that have 95% identity to 20-455 nucleotides of SEQ ID NO:1 and have any function In contrast, the specification only describes the region between -1000 and -600 or -700 bp of the NtQPT1 promoter; where this is located on SEQ ID NO:1 is unclear. It is also unclear

if the region is sufficient to reduce the amount of nicotine in a plant. Applicant does not describe other DNA molecules encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

No function is provided for the nucleic acids with 95% identity to 20-455 nucleotides of SEQ ID NO:1; thus, written description is further lacking for the molecules.

Hence, Applicant has not, in fact, described DNA molecules that that comprise 20-455 nucleotide fragments of SEQ ID NO:1 or that hybridize to SEQ ID NO:1, wherein the DNA molecule is a *Nic* gene product responsive element and wherein the DNA molecule is sufficient to reduce the amount of nicotine in a plant, within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

Applicant urges that rejection of an original claim for lack or written description should be rare (response pg 21).

This is not found persuasive. Just because such a rejection should be rare does not mean it should not be made when appropriate.

Applicant urges that one of skill in that art can readily envision fragments comprising the amino acid sequence of SEQ ID NO:1 [sic] or active fragments thereof and that one of skill in the art could readily search the Patent Office nucleotide database to determine the region of the promoter; quick search of US 5,837,876 shows that the sequence is found in SEQ ID NOs:1 and

3-5 in that patent. Thus, Applicant argues that they were in possession of the claimed genus (response pg 21).

This is not found persuasive. The Patent Office nucleotide database is not available to the public because it contains proprietary information; thus, one of skill in the art could not readily search it. Furthermore, neither the instant specification nor '876 describes 20 nucleotide long, or any other fragment of SEQ ID NO:1 that functions as a molecular decoy to reduce the amount of nicotine in tobacco plant.

9. Claims and 5-9 and 14-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is modified from the rejection set forth in the Office action mailed 29 July 2004, as applied to claims 1-32, due to Applicant's amendment of the claims. Applicant's arguments filed 30 January 2004 have been fully considered but they are not persuasive.

Claims 14 and 25 are indefinite in their recitation of "responsive to a *Nic* gene product" in part (c). It is unclear what is means for a nucleic acid to be responsive to a *Nic* gene product. What does it do to "respond" to it? If the *Nic* gene product binds to the nucleic acid, it is the *Nic* gene product that responds to the nucleic acid - the nucleic acid itself does not do anything to "respond" to the gene product.

Applicant urges that the phrase "responsive to a Nic gene product" is defined to mean, for example, "increase or decrease transcription of an operatively associated gene and hence

increase or decrease the level of the encoded protein of interest in the host cells" (response pg 22).

This is not found persuasive because it is unclear what is means for a nucleic acid to be responsive to a *Nic* gene product. If the *Nic* gene product binds to the nucleic acid, it is the *Nic* gene product that responds to the nucleic acid - the nucleic acid itself does not do anything to "respond" to the gene product.

Claim 5 is indefinite in its recitation of "isolated nucleic acid according to claim 1, further comprising a recombinant nucleic acid construct". The claim should be rewritten to claim a recombinant nucleic acid construct comprising the nucleic acid of claim 1. As currently written, it is not clear if the nucleic acid is part of the recombinant nucleic acid construct or merely attached to it.

Applicant urges that the claim has been amended to recite a recombinant nucleic acid construct (response pg 23).

This is not found persuasive because claim 5 has not been so amended.

Claims 23 and 32 are indefinite because it is not clear if the tobacco seed comprises the Nic gene product responsive element. Not all progeny seed will comprise the nucleic acid with which their parent as transformed.

Applicant urges that the claim has been amended (response pg 7).

This is not found persuasive because it is not clear if the seed comprises only one copy of the element or if it contains as many copes as was transformed into the plant cell in the method of claim 11 or is present in the plant of claim 24.

Claim 24 is indefinite in its recitation of "exogenous" in line 2 and claims 27 and 29 are indefinite for the word in line 1.

Applicant urges that an exogenous construct comprising an Nic gene product responsive element may be introduced into a tobacco plant cell; thus the nucleic acids may be exogenous to the tobacco plant (response pg 23-24).

This is not found persuasive because the claim states the exogenous nucleic acid consists essentially of a Nic gene product responsive element; *Nic* gene product responsive elements are tobacco nucleic acids, so it is not clear how these nucleic acids could be exogenous to the tobacco plant. The claim is not drawn to plants transformed with construct comprising a Nic gene product responsive element.

The following rejections are new, due to amendment:

Claims 6-7 and 9 lack antecedent basis for the limitation "The recombinant nucleic acid construct according to claim 5" as claim 5 is drawn to an isolated nucleic acid.

Claim 8 lacks antecedent basis for the limitation "The isolated nucleic acid construct according to claim 1" as claim 1 is drawn to an isolated nucleic acid.

Claim Rejections - 35 USC § 102

10. Claims 1-10 remain rejected under 35 U.S.C. 102(b) as being anticipated by Conkling et al (WO 97/05261). The rejection is repeated for the reasons of record as set forth in the Office action mailed 29 July 2004. Applicant's arguments filed 30 January 2004 have been fully considered but they are not persuasive.

Applicant urges that WO 97/05261 fails to disclose an isolated nucleic acid that anticipates each and every element of claim 1 (response pg 24-25).

This is not found persuasive because Conkling et al teach recombinant nucleic acid constructs comprising SEQ ID NO:1 and tobacco plants transformed with them via *Agrobacterium* -mediated transformation (pg 19-22 and Figure 3). The nucleic acid would be linear in the transformed plants. Furthermore, Applicant stated that "the sequence is found in U.S. Patent 5,837,876 in the 2010 base pair sequence (SEQ ID NO:1) of the 5' region of TobRD2, and that it may be found in the A1 .4 promoter (SEQ ID NO:3) with GUS; A1.3 promoter (SEQ ID NO:4) with GUS; and the A1.0 promoter (SEQ ID N0:5) with GUS" on pg 21-22 of the response.

Double Patenting

11. Claims 1-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 16-22 of U.S. Patent No. 5,837,876. The rejection is repeated for the reasons of record as set forth in the Office action mailed 29 July 2004. Applicant's arguments filed 30 January 2004 have been fully considered but they are not persuasive.

Applicant urges that the sequence of claim 1 is not the same as SEQ ID NO:1 of '876, nor are the claims obvious in view of '876 (response pg 25).

This is not found persuasive because Applicant stated that "the sequence is found in U.S. Patent 5,837,876 in the 2010 base pair sequence (SEQ ID NO:1) of the 5' region of TobRD2, and that it may be found in the A1 .4 promoter (SEQ ID NO:3) with GUS; A1.3 promoter (SEQ ID

NO:4) with GUS; and the A1.0 promoter (SEQ ID N0:5) with GUS" on pg 21-22 of the response.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
April 6, 2004

ANNE KUBELIK
PATENT EXAMINER